April 5, 2019

Via Federal Express

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Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20004

Dear 8(e) Coordinator:

Test substance:

8EHQ-19-21622

1-Propene, 1,1,2,3,3,3-hexafluoro-
CAS RN 116-15-4

This letter is to inform you of the results of the following Inhalation extended one-generation reproduction toxicity study with the above-referenced test substance. This information is submitted in accordance with current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act or, where it is not clear that reporting criteria have been met, because it is information in which EPA may have an interest.

Summary:

The objective of this study was to provide data on the possible effects of the test substance hexafluoropropene (hexafluoropropylene (HFP)) on reproductive performance of Wistar rats and the development of pups consequent to daily inhalation exposure to various concentrations of the test substance (intended target concentrations: 0 ppm, 50 ppm, 300 ppm and 900 ppm[1]) to male and female rats during a premating period of 10 weeks and during mating (max. 2 weeks), gestation and lactation until postnatal day (PN) 21. At weaning on postnatal day 21 (PN 21), pups were distributed to Cohorts 1A and 1B and were exposed to the test substance at lower concentrations than their parents during their growth into adulthood (intended target concentrations: 0 ppm, 50 ppm, 300 ppm and 600 ppm[2]).

Exposure
The overall average actual concentration (± standard deviation) of HFP in the low- concentration test atmosphere (group 2; 50 ppm target concentration), as determined by total carbon analysis, was 49.3 (± 2.1) ppm. Exposure to the mid-concentration (group 3) was started at a target concentration of 300 ppm, which was reduced to 100 ppm as of 3 June 2018; the average actual concentrations were 300.3 (± 7.9) and 100.3 (± 1.2) ppm, respectively.

[1] Since several animals of the high-concentration group (900 ppm) were found dead during the first days of exposure, the target concentration of the high-concentration group was lowered to 600 ppm for ethical reasons starting on 10 February 2018 (after five days of exposure to 900 ppm). The animals that died were replaced by surplus animals (Amendment 1 (Annex 13) and Annex 3 Cross referencelist).

[2] Since mortality was observed in the F1-animals (selected pups for Cohorts 1A and 1B) after 2 exposure days in mid- and high-concentration groups (300 and 600 ppm, respectively), the target concentrations of these exposure groups were lowered to 100 ppm for the mid-concentration group and to 200 ppm for the high-concentration group. This included both the exposure of F1 animals in Cohorts 1A and 1B as well as the exposure of the F0 females in the last week up to sacrifice. Dead F1-animals were replaced by spare animals, which were exposed from 3 or 6 June 2018 onwards (Amendment 3 (Annex 13) and Annex 3 Cross reference list).

Average concentrations in the high-concentration test atmosphere (group 4) were 900.3 (± 12.9), 601.0 (± 19.5) and 199.8 (± 2.4) ppm, in the periods 5-9 February, 10 February – 2 June, and 3 June – 29 August 2018 when target concentrations were 900, 600 and 200 ppm, respectively.

General Observations in Parental (F0) Animals and F1-Generation Animals after Weaning

Three F0-females of the high-concentration group (900 ppm) and several animals of Cohorts 1A and 1B of the high-concentration groups (600 ppm) died during the first days of exposure. Accordingly, the target concentration of the high-concentration group was lowered during exposure of the F0-generation (from 900 ppm to 600 ppm) and the target concentrations of the mid- and high-concentration groups of the F1-generation were lowered before the start (day 0) of Cohort 1A and Cohort 1B (from 300 ppm to 100 ppm and from 600 ppm to 200 ppm, respectively). Animals that died were replaced by surplus animals and after lowering the target concentrations, no other animals died during the study.

Clinical observations revealed piloerection, hunched posture, respiration dyspnoea and/or muscle weakness in several animals of the high-concentration group during the first exposure days of the F0-generation and in the first exposure weeks of Cohort 1A and 1B. These signs were mainly observed in the high-concentration group (900 ppm) of the F0-generation and in the high-concentration group (600 ppm) of Cohorts 1A and 1B, before lowering the target concentrations and disappeared thereafter. No other treatment-related (detailed) clinical signs were observed during the study.

In the F0-generation, body weights of the male animals of the mid- and high-concentration groups and in females of the high-concentration group were statistically significantly lower than the corresponding control animals (maximally, during premating: F0 males 17%, F0 females 10%; F0 females during gestation 9%, F0-females during lactation 7%).

In Cohorts 1A and 1B of the F1-generation, body weights were statistically significantly lower in the males and females of the mid- and high-concentration groups (in Cohort 1A maximally 30% in males and 28% in females, respectively, and in Cohort 1B maximally 35% in males and 30% in females, respectively).

In the F0-generation, food consumption of the male and female animals of the high- concentration group was statistically significantly lower than of the control animals (maximally 44% in males and 39% in females). In male and females animals of the mid-concentration groups food consumption was statistically significantly lower compared to control animals during the first week(s) of the study.

In the F1-generation, food consumption of the male and females animals of the high- concentration group was statistically significantly lower than of controls (in Cohort 1A maximally 25% in males and 18% in females, respectively, and in Cohort 1B maximally 22% in males and 16% in females, respectively).

The observed effects on body weights were considered, at least in part, as transient and/or as related to the lower food consumption. The observed effects on body weights in the high- concentration groups of the F0- (600 ppm) and F1-(200 ppm) generations, however, were considered to be related to treatment.

Except for the increase in urea in male animals of the high-concentration group of the F0- generation (68% higher than controls) and in male animals of the high-concentration group of Cohort 1A of the F1-generation (18% higher than controls), no treatment-related effects were observed on hematology and clinical chemistry parameters.

Urinalysis revealed a higher urinary volume in males of the low-, mid-and high-concentration groups of the F0-generation and in females of the high-concentration group of Cohort 1A of the F1-generation.

In the F0-generation, the increased relative kidney weight in male and female animals of the mid-and high-concentration groups (300-600 ppm: ~91-130% increase in males and ~44- 65% increase in females compared to controls, respectively) were considered to be adverse and related to treatment. Additionally, in F0-generation animals, terminal body weight was decreased in males of the mid- and high-concentration groups (300 and 600

ppm; maximally 17% below controls). Furthermore, the increased relative lung weight (~19-30% in males and ~14% in females), heart weight (~20-39% in males and ~22% in females), liver weight (~15-18% in males and ~14% in females), and spleen weight (~10-21% in males and ~13% in females) as observed in male animals of the mid- (300 ppm) and high-concentration (600 ppm) groups and in female animals of the high-concentration group (600 ppm) were considered to be related to treatment.

In Cohort 1A of the F1-generation, the increased relative kidney weight in male and female animals of the mid-and high-concentration groups (100-200 ppm: ~17-58% increase in males and ~20-51% increase in females compared to controls, respectively) were considered to be adverse and related to treatment. Additionally, in Cohort 1A animals, terminal body weight was decreased in high-concentration (200 ppm) male and female animals (decrease of 13% and 12%, respectively). Furthermore, the increased relative lung weight (~7-13% in males and ~6-10% in females) and relative liver weight (~9-13% in males and ~7-11% in females) as observed in males and females of the mid- (100 ppm) and high concentration (200 ppm) groups and the increased relative heart weight observed in high-concentration (200 ppm) males and mid- (100 ppm) and high-concentration (200 ppm) females (~13% and 15%, respectively) were considered to be related to treatment.

No effects were observed on the weight of the reproductive organs of Cohort 1B F1-generation animals.

At necropsy, macroscopic examination revealed pale discoloration, enlargement and/or a pitted surface of the kidneys in mid- and high-concentration animals of the F0-generation (300 ppm and 600 ppm) and in animals of Cohort 1A of the F1-generation (100 ppm and 200 ppm).

Microscopic examination of the sampled organs and tissues in the F0-generation animals revealed treatment-related histopathological changes in the heart (minimal to moderate ventricular muscle degeneration) in high-concentration females (600 ppm) and kidneys (minimal to moderate tubular dilatation, mononuclear inflammation, proteinaceous casts and/or basophilic tubules) in mid- and high-concentration animals (300 and 600 ppm, respectively).

Microscopic examination of the sampled organs and tissues of the animals of Cohort 1A of the F1-generation revealed treatment related histopathological changes in the kidneys (minimal to moderate tubular dilatation, mononuclear inflammation, proteinaceous casts and/or basophilic tubules) in mid- and high-concentration animals (100 and 200 ppm, respectively).
Other organs and tissues did not reveal treatment related histopathological changes.

Fertility and Reproductive Parameters
No treatment-related effects were observed on the fertility and reproductive performance of male and female animals of the F0-generation.

No treatment-related effects were observed on estrus cycle related parameters in female animals of the F0-generation and in animals of Cohort 1A of the F1-generation.

No treatment-related effects were observed on epididymal and testicular sperm parameters in male animals of the F0-generation and in animals of Cohort 1A of the F1-generation.

No effects were observed on TSH and T4 analysis in animals of the F0-generation and in adult F1-generation animals of Cohort 1A.

General- and Sexual-Developmental Parameters
No treatment-related effects were observed on number of live pups, number of implantation sites, implantation loss, stillborn pups, dead, missing and/or cannibalized pups, litter loss, pup viability indices and sex ratio.

No treatment-related effects were observed on clinical signs of pups nor on macroscopic observations at sacrifice and of dead pups in F1-generation pups.

Overall, in the mid- (300 ppm) and high-concentration group (600 ppm), the body weight of F1-generation pups during the lactation period was lower than of the corresponding control pups (~10-15% on postnatal day 21). This finding was considered to be related to treatment.

No direct effects were observed on anogenital distance on PN4 in F1-generation pups or on nipple retention in male F1-generation pups.

Preputial separation (control: 42.4 days, high dose 46.4 days) was delayed in male pups of the high-concentration group (200 ppm). However, these differences were not considered as delayed sexual development but as a consequence of delayed general development (lower pup weights).

At sacrifice of the selected pups at post-natal day 21, the terminal body weights of the pups of the mid-concentration (300 ppm) and high-concentration (600 ppm) groups calculated per litter were lower than of the control group. No direct effects were observed on organ weights of F1-generation pups sacrificed on post-natal day 21.

No treatment-related effects were observed on the development of the ovarian follicles from primordial small follicles into corpora lutea in Cohort 1A animals of the F1-generation.

No treatment-related effects were observed on splenic lymphocyte subpopulation analysis in Cohort 1A animals of the F1-generation.

Overall Conclusion:

General Toxicity – Parental Generation (F0-Animals)
Based on the decreased body weights (change), decreased food consumption, increased urinary volume, effects on organ weights, macroscopic observations in the kidneys and microscopic effects in several organs (kidneys, heart and thymus) the No Observed Adverse Effect Concentration (NOAEC) for parental toxicity was placed at the low-concentration (50 ppm) hexafluoropropene (HFP) after exposure via inhalation for 6 hours/day, 7 days/week for up to 12 weeks for males (pre-mating through mating) and for 12 weeks for females (pre- mating through mating) and then through post-natal day (PND) 21.

Fertility and Reproductive Performance
There were no treatment-related adverse effects of hexafluoropropene (HFP) exposure on any of the multiple endpoints assessed with regards to fertility and reproductive performance in the parental generation (F0-animals). In addition, there also were no treatment-related adverse effects on the various reproductive systems endpoints assessed in the male and female F1-animals (Cohorts 1A and 1B).

Based on the absence of any treatment-related adverse effects on any fertility and reproductive performance parameters in this OECD 443-compliant study, the study NOAEC for fertility and reproductive performance was placed at the high-concentration (600 ppm) of hexafluoropropene (HFP).

General- and Sexual-Developmental of F1-Generation Animals
Based on the increased relative organ weights (kidney, lung, liver, heart) and the histopathological changes in the kidney after macroscopic and microscopic examination in mid- (100 ppm) and high-concentration (200 ppm) animals of Cohort 1A, the No Observed Adverse Effect Concentration (NOAEC) was based on these general toxicity observations and placed at the low-concentration (50 ppm) hexafluoropropene (HFP). There were no treatment-related effects on sexual development at any exposure concentration in the F1-generation animals.

I hereby certify to the best of my knowledge and belief that all information entered on this form is complete and accurate.

I further certify that, pursuant to 15 U.S.C. § 2613(c), for all claims for confidentiality made with this submission, all information submitted to substantiate such claims is true and correct, and that it is true and correct that

(i) My company has taken reasonable measures to protect the confidentiality of the information;

(ii) I have determined that the information is not required to be disclosed or otherwise made available to the public under any other Federal law;

(iii) I have a reasonable basis to conclude that disclosure of the information is likely to cause substantial harm to the competitive position of my company; and

(iv) I have a reasonable basis to believe that the information is not readily discoverable through reverse engineering.

Any knowing and willful misrepresentation is subject to criminal penalty pursuant to 18 U.S.C. § 1001.

Substantiation of our claim of confidentiality is included herewith as **Attachment 1**. Please contact me if you have any questions about this submission or need further clarification.

Sincerely,

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Attachment 1

Entire Substantiation Claimed as Confidential Business Information